Obstructive sleep apnea – a new tobacco-related disease?

Sindromul de apnee în somn de tip obstructiv – o nouă patologie secundară fumatului?

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Abstract

Introduction. *Smoking and obstructive sleep apnea syndrome (OSA) have in common hypoxia and premature aging, both having a growing prevalence. Smoking is a risk factor for OSA onset, increases OSA severity, amplifies comorbidities, and causes a vicious circle, increasing morbidity and mortality. The aim of our research was to assess the impact of smoking on OSA.*
Materials and methods. *A 42-month transversal study of OSA prevalence and comorbidities (cardiovascular, metabolic, COPD and asthma) was performed among 326 adults, with sleep breathing complaints, based on clinical and paraclinical data, including Body Mass Index (BMI), Epworth and Tobacco Smoke-Exposure (TSE) questionnaires and overnight cardio-respiratory polygraphy. Apnea-hypopnea index (AHI) of ≥5 obstructive events/hour of sleep was the main criteria for OSA diagnosis.*
Results. *228 of 326 adults, with age ≥50 years old (67%), male gender (73%), and TSE (65.64%) were diagnosed with sleep disorder breathing (SDB). The high mean value of AHI (33.01) was influenced by the decade of age (p=0.005). Oxygen desaturation index (ODI) by hour of sleep correlated with TSE and OSA associated diseases (p<0.05), BMI, obesity and AHI (p<0.01). The prevalence of OSA was increased among SDB patients (89.47%) and smokers (64.48%). OSA was two times more frequent in smokers versus other SDB (p<0.0000003), especially in heavy smokers (p=0.045). Severe OSA related smoking was revealed by high mean values of AHI (p=0.032) and ODI (p=0.017), being 2.2 times more frequent in heavy and moderate smokers (p<0.007). Heart disease, COPD and asthma associated to OSA were significantly influenced by TSE (p<0.03). The means of AHI and ODI are significantly increased in smokers with OSA and without COPD (n=50) versus nonsmokers (n=100) for F=32.417; p=0.000; respectively F=29.417; p=0.000, with no influence of BMI (F=3.786; p<0.06). In conclusion, OSA occurence, prevalence and severity are related to smoking.*
Keywords: *COPD, OSA, AHI*

Rezumat

Introducere. *Fumatul și sindromul de apnee obstructivă în somn (SASO) au în comun hipoxia și îmbătrânirea precoce, cu prevalență în creștere. Fumatul este un factor de risc important în apariția SASO, contribuie la creșterea severității acestei afecțiuni, amplifică expresia comorbidităților SASO și induce un cerc vicios ce contribuie la creșterea morbidității și mortalității. Scopul acestui studiu a fost evaluarea impactului fumatului asupra SASO.*
Material și metodă. *Un studiu transversal de prevalență a SASO în funcție de expunerea la fumat și de comorbiditățile asociate (cardiace, metabolice, BPOC și astm), pe durata a 42 de luni, s-a efectuat la un număr de 326 de adulți, cu acuze respiratorii în somn, pe baza datelor clinice (indicele de masă corporală [IMC], chestionarele Epworth și de expunere la fumat) și paraclinice (metoda poligrafică cardiorespiratorie nocturnă). Criteriul principal pentru diagnosticul SASO a fost reprezentat de indicele apnee-hipopnee (IAH) de ≥5 evenimente obstructive/ora de somn.*
Rezultate. *228 din cei 326 de adulți, cu predominanța vârstei egală sau peste 50 de ani (67%), a sexului masculin (73%) și a fumatului (65,64%), au fost diagnosticați cu tulburări respiratorii în timpul somnului. Valoarea medie a IAH a fost crescută (33,01/ora de somn), fiind influențată de decada de vârstă (p=0,005). Indicele de desaturare (ID)/ora de somn s-a corelat cu bolile asociate SASO și fumat (p<0,05), IMC, obezitatea și IAH (p<0,01). Prevalența SASO a fost crescută în rândul pacienților cu tulburări respiratorii în timpul somnului (89,47%) și a fumătorilor (64,48%). SASO a fost de două ori mai frecvent la fumători versus pacienți cu alte tulburări respiratorii din timpul somnului (p<0,0000003), în special la marii fumători (p=0,045). Formele severe ale SASO s-au corelat cu fumatul, cu valori medii ridicate ale IAH (p=0,032) și cu ID (p=0,017), fiind de 2,2 ori mai frecvente la marii fumători (p<0,007). Bolile cardiace, BPOC și astmul asociate SASO au fost influențate semnificativ de fumat (p<0,03). Valorile medii ale IAH și ID apar semnificativ crescute la fumători cu SASO, dar fără BPOC asociat (n=50), versus nefumători (n=100) (F=32,417; p=0,000; respectiv F=29,417; p=0,000), fără influența IMC (F=3,786; p<0,06). În concluzie, apariția, prevalența și severitatea SASO sunt influențate de fumat.*
Cuvinte-cheie: *SASO, BPOC, IAH*

Background

Sleep is essential to life. Occupying nearly one-third of an adult's life, it has a considerable impact on the quality of life. Changes in the quality of sleep and reduction of the number of hours of sleep throughout lifetime are more and more frequent in modern society and are accompanied by negative systemic effects. Statistics show that nearly 1 billion inhabitants of the world do not have a physiological sleep[(1)]. Sleep issue has been a concern of great philosophers and physicians of the world since Aristotle and Hippocrates, but there is not yet a complete definition that brings together all the characteristics of sleep disorders[(2)]. Exhaustively, it can be said that "sleep disorders are a heterogeneous group of disorders capable of generating discomfort"[(1)]. Sleep medicine started in 1965, after the discovery of obstructive sleep apnea (OSA) in 1965[(3)]. OSA became a frequent syndrome with an estimated prevalence of 2-5% in general population, characterized by "pauses or apneas at least 10 per hour of sleep, with intermittent hypoxemia, sleep destruction, hypersomnolence and serious neurohumoral and metabolic imbalances"[(4)]. Following the discovery of continuos positive airway pressure therapy (CPAP) through nasal mask, in 1981[(5)], the characteristics and consequences of OSA were considered, after insomnia, the sleep disturbance with the highest prevalence in the general population, more common in males (24%) and middle-aged women (9%)[(6)]. Risk factors

and SAS comorbidities are not fully identified, but cardiovascular diseases (treatment-resistant hypertension, arrhythmias, myocardial infarction, sudden death)[7,8], metabolic diseases (obesity and diabetes), obstructive lung diseases (COPD and asthma), neurological diseases, psychiatric disorders[9] are considered pathological consequences. Smoking and OSA are prevalent disorders, both with a significant impact on morbidity and mortality[10]. It has been hypothesized that each of these negative conditions leads to an increase in comorbidities[11] However, although the association between smoking and OSA is plausible, there are not enough studies on the impact of smoking on OSA, and the current evidence is still on debate.

The aim of this study was to assess the prevalence of smoking and OSA comorbidities among patients with various sleep complaints and disorders, the impact of smoking on OSA occurrence and severity, and the relationship between smoking and OSA comorbidities.

Material and methods

The research evaluated the impact of smoking on sleep pathology among a sleep lab population of 326 adults with complaints of breath-related disorders during night time sleep. All subjects were investigated, over a 42-months period, from October 2011 to April 2015, in two sleep laboratories, in Constanţa, Romania, overnight cardio-respiratory polygraphy after obtaining informed consent. The transversal statistical study analyzed the prevalence of OSA, isolated and related with smoking, and comorbidities (cardiovascular, metabolic, COPD and asthma). The patients were clinically and paraclinically evaluated for various sleep disordered-breathing (SDB), including Epworth questionnaire and somnolence scale. The spectrum of SDB was identified with the assessment of personal history of snoring and witnessed apnea during night time sleep, difficulty with nocturnal sleep maintenance with unrefreshing sleep, excessive nicturia, morning headaches, excessive daytime sleepiness (EDS), difficulty with concentration, memory loss (short-term), impaired cognition, irritability, mood disorders and decreased libido. The physical exam of patients with reported sleep complaints was focused on neck and waist circumference measurements, facial skeletal abnormalities like retrognathia or micrognathia, nasal deformities/septal deviation, enlarged tonsils, high-arched hard palate, and Body Mass Index (BMI) evalution. Home sleep recordings were performed by STARDUST II portable device and scored respecting criteria of Rechtschaffen and Kales[12]. Apneas were defined as "cessation of oronasal airflow lasting ≥10 seconds" and hypopneas as "airflow reduction of >50%, compared with a 10-second peak amplitude during the preceding 2 minutes, lasting ≥10 seconds and associated with oxygen desaturation of ≥3%"[13]. The diagnosis of OSA sustained by an "apnea-hypopnea index (AHI) of ≥5 obstructive events/hour of sleep" and the severity criteria of OSA were based on the guidelines of American Academy of Sleep Medicine 2014 (mild OSA in patients with 5≤AHI≤15; moderate OSA in patients with 15≤AHI≤30, and severe OSA in patients with AHI>30 obstructive events/hour of sleep)[14]. The oxygen desaturation index (ODI) is "the value of arterial oxygen desaturations of ≥3% respiratory events per hour of sleep"[15]. The comorbid conditions of OSA like arterial hypertension (mainly resistant hypertension), recurrent atrial fibrillation, stroke, myocardial infarction, pulmonary hypertension, chronic heart failure, metabolic syndrome, COPD and bronchial asthma were assessed based on smoking exposure (present or absent, former or current smoking), and amplitude (mild, moderate and high).

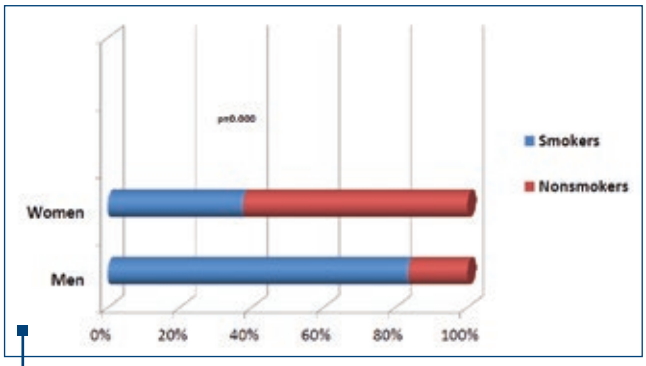

Figure 1. *The structure of TSE among cases with sleep complaints by gender*

Tobacco smoke-exposure (TSE) questionnaire was aplied and allowed, by quantification of the number of pack year (PA) of smoked cigars, the identification of never smokers (NS), mild smokers (<10 PA), moderate smokers (10-19 PA) and heavy smokers (≥20 PA). OSA prevalence was assessed among cases related to TSE. ANOVA analysis of variance of AHI and ODI means was performed in groups of OSA with and without COPD by smoking. The impact of COPD on the severity of OSA was also determined according to AHI and ODI values.

The statistical analysis was performed by using version 20 of IBM SPSS Program, respecting 95% confidence intervals (CI) as measures of association between smoking and OSA.

Results

Sleep laboratory screened cases consisted in 326 adults with an average age of 53.15 years +/-11.436 standard deviations (ranging from 20 to 83 years old). The mean age of males (51.82+/-11.419 [limits: 20-83 years]) was significantly lower versus females (56.70+/-10.763 [limits: 20-79 years]), according to ANOVA test (F=12.156; p= 0.001).

The demographic characteristics of cases consisted in the predominance of age ≥50 years old (n=219/326; 67.17%), male gender (n=237/326; 73%), urban provenience (n=311/326; 95,4%) and TSE (n=214/326; 65.64%; 179 males versus 35 females; with a high gender ratio of smokers in the favour of males [M/F=5.11], RR=1.6152; 1.3380<RR<1.9498; 2.8358<OR<7.9952; χ^2=37.4839; p=0.000) – Figure 1. The professional structure of the subjects included 155 employees (47.5%), 134 retirees (41.1%) and 37 persons without occupation (11.3%).

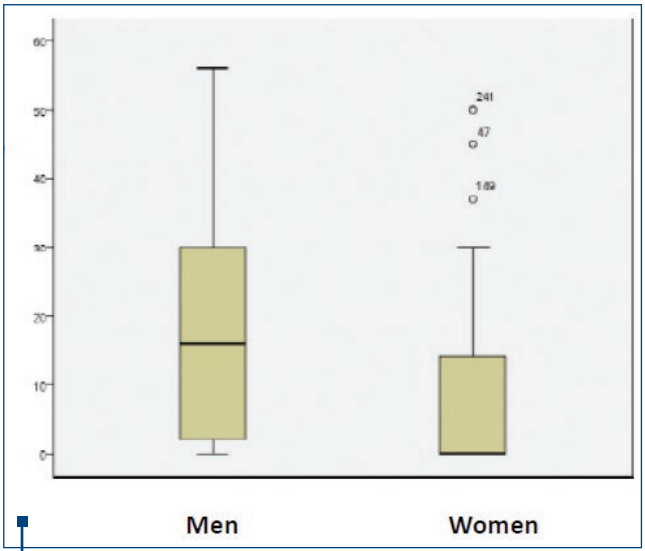

Figure 2. *The average number of yearlly smoked cigarette packs by gender of cases*

TSE questionaire clasified cases in 112 nonsmokers, 26 mild smokers, 56 moderate smokers and 132 heavy smokers (χ^2= 38.988; p=0.000). TSE cases were divided into 121 current smokers (37.1%), 93 former smokers (28.5%), with obvious male predominance (n=179) among current (n=97/121; 80.16%) and former smokers (n=82/93, 88.17%). The average number of yearly smoked cigarette packs was 14.24 (limits from 2 to 56), being twice higher in males versus females, with significant differences by gender according to the ANOVA test (16.82 versus 7.37; F=34.49, p=0.000) – Figure 2.

The Epworth questionnaire provided data on the risk of excessive daytime somnolence (SDE) at a total score ≥10 points at 37.81% (n=116/326) of patients. This somnolence scale had an average of 8.35 points +/-5.211 std. dev. (limits: 0-25) without gender (8.34 points +/-5.296 std. dev. [limits: 0-25] in men versus 8.37 points +/-5.008 std. dev. [limits: 2-24] in women [F=0.003; p=0.959]) and age differences (F=1.961, p=0.084) – Table 1.

Body Mass Index (BMI) had a mean of 33.73 kg/m^2 +/-6.51 std. dev. (limits: 18.36-59.50 kg/m^2), with no differences depending on the gender of cases (33.509 kg/m^2 +/-6.257 std. dev. [limits: 21-59.50 kg/m^2] in men versus 34.34 kg/m^2 +/-7.15 std. dev. [limits: 18.36-49.50 kg/m^2] in women), according to ANOVA variance analysis (F=1.054; p=0.305). By smoking, it was better correlated with OSA and comordities (p=0.01) than isolated OSA (p=0.111).

Sleep disturbances with polygraphic screening were various, with polymorphic symptoms usually associated, consisting in snoring (n=323/326; 99.1%), nighttime sleep apnea (n=265/326, 81.3%), nicturia (n=197/326, 60.4%), nocturnal paroxistic dyspnea (n=161/326, 49.38%), morning headache (n=121/326, 37.1%) and daytime somnolence (n=116/326; 37.81).

The Mallampati score had a mean value of 0.64+/-1.135 (limits: 0-4), without differences by gender (F=0.11; p=0.918). Neck circumference had an average value of 43.15 cm +/-3.515 (limits: 36-53) with elevated values in men (F=89.482; p=0.000) and older age ≥50 years (F=2.726, p=0.20). The waist circumference oscillated between 88 and 173 cm, with a mean of 108 cm +/-10.789 std. dev., and had significantly elevated values in men (110.02+/-40.405) versus women (105.03+/-11.012) (F=14.3741; p=0.000), and no statistical differences depending on age decade (F=2.170; p=0.057).

The average of apnea hipopnea index (AHI) by hour of sleep was 33.01±27.088 std. dev. (limits: 1-135), with differences by decade of age (F=3.464; p=0.005) and no one by gender (F=3.483; p=0.063). AHI was significantly correlated with BMI and obesity (P two tailed <0.01).

The oxygen desaturation index (ODI) by hour of sleep had a mean value of 34.60601+/-29.277 std. dev. (limits: 0.5-150.9), influenced by gender (F=4.833, p=0.029) and age (F=3.546, p=0.004). ODI correlated significantly statistically with tobacco smoke exposure, OSA associated diseases (p<0.05), BMI, obesity and AHI (p<0.01).

The mean nocturnal oxygen saturation of arterial blood (mean SaO_2) was 92.14+/-3.933 std. dev. (limits: 75-97), while the mean of minimal SaO_2 recorded was 76.37+/-8.465 std. dev. (limits: 60-94), with no statistically significant differences by gender (F=0.544; p=0.461 for minimal SaO_2, respectively F=0.250; p=0.618 for mean SaO_2) and age decade (F=1.145; p=0.336 for minimal SaO_2, respectively F=0.324; p=0.898 for mean SaO_2). Average and minimal SaO_2 correlated statistically significant with diabetes mellitus (p=0.05), BMI, obesity, AHI and ODI (p<0.01).

The relative risk of SDB occurence was increased in men (RR=1.6152; 1.3380<RR<1.9498; c^2=37.4839; p=0.000). The prevalence of OSA was increased among patients with SDB (n=204/228; 89.47%) and TSE (n=138/214; 64.48%). OSA was two times more frequently diagnosed in smokers (n=138) versus nonsmokers (n=66), compared with other SDB more frequent in nonsmokers (n=76) versus smokers (n=46) (OR=3.4545; RR=1.6136; c^2=26.6353; p<0.0000003). The causes of non-OSA disorders were 4.38% central apnea and 6.14% obesity hipoventilation syndrome.

The average values of neck and waist circumference were significant increased in smokers (p=0.000; Figure 3), OSA (p=0.000), obesity (p=0.000), metabolic syndrome (p=0.001), excessive diurnal sleepiness (p=0.000), unlike the Mallampati score that did not differ statistically significantly. In snoring subjects, however, all these variables did not show statistically significant differences (0.3<p<0.4).

The Epworth average score did not appear to be influenced by smoking (8.67+/-5.137 std. dev. [limits: 0-24] in smokers versus 7.73+/-5.252 [limits: 1-25] in non-smokers, F=2.382; p=0.124), except for associated obesity (9.19+/-5.398 dev. [limits: 1-25] in 226 obese subjects versus 6.45+/-4.205 [limits: 0-20] in 100 non-obese individuals; F=20.238; p=0.000), and OSA (9.15+/-5.382 std. dev. [limits: 0-25 points] in 204 patients versus 7+/-4.628 [limits: 1-22] among 122 patients without OSA [F=13.520, p=0.000]).

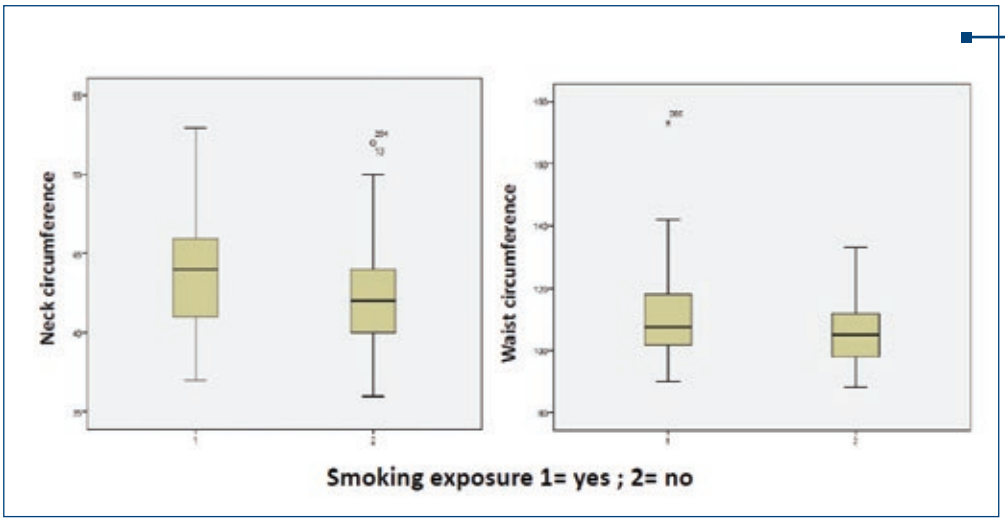

Figure 3. *Anthropometric measurements of neck and waist circumference in cases by tobacco smoke exposure*

Table 1 The distribution of Epworth Score among patients with SDB by decade of age

Decade of age (years)	Mean	Number	Std. Deviation	Minimum	Maximum
20-29	9.80	10	6.197	2	22
30-39	7.97	37	6.436	1	25
40-49	9.43	60	5.450	1	22
50-59	8.87	108	4.876	0	24
60-69	7.27	97	4.795	1	21
≥70	7.07	14	4.141	2	16
Total	**8.35**	**326**	**5.211**	**0**	**25**

Table 2 The impact of smoking on OSA and comorbidities by the magnitude of Tobacco Smoke Exposure

Tobacco Smoking Exposure	OSA		HI		Heart disease		COPD		Asthma		Metabolic Syndrome	
	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
Nonsmokers	66	46	71	41	39	73	8	104	19	93	13	99
Mild smokers < 10 Pack year	11	15	10	16	6	20	2	24	3	23	4	22
Moderate smokers 10-19 Pack year	35	21	29	27	7	49	11	45	2	54	6	50
Heavy smokers ≥ 20 Pack year	92	40	84	48	39	93	52	80	8	124	3	26
Total	**204**	**122**	**194**	**132**	**91**	**235**	**73**	**253**	**32**	**294**	**49**	**277**
χ^2 tests	χ^2=8.056		χ^2=7.801		χ^2=9.745		χ^2=40.419		χ^2=11.122		χ^2=4.098	
	p=0.045		p=0.050		p=0.021		p=0.000		p=0.011		p=2.51	

The impact of smoking on OSA was revealed by a greater prevalence of smoking in OSA patients (n=138/204; 67.64%), and OSA related to the magnitude of TSE (69.69% in heavy smokers (n=92/132) versus 62.5% in moderate smokers (n=35/56), 42.3% in mild smokers (n=11/26) and 58.9% in nonsmokers (n=66/112) (Table 2), and OSA severity revealed by high mean values of AHI (F=2.976; p=0.032) and ODI (F=3.445; p=0.017). The severe forms represented more than half of OSA cases (n=141/204; 69.11%), being 2.2 times more frequent in heavy (n=72/92; 79.11%) and moderate smokers (n=25/35; 71.42%) than in mild (n=7/11; 63.63%) and non-smokers (37/66; 56%) (OR=2.425; 95% CI: 1.3184-4.4604; RR=1.3366; 95% CI: 1.0767-1.6593; c^2=7.434; p<0.007) – Figure 4. The comobidities of both smoking and/or OSA, as heart disease, COPD and asthma, were significantly influenced by TSE (p<0.03) – Table 2.

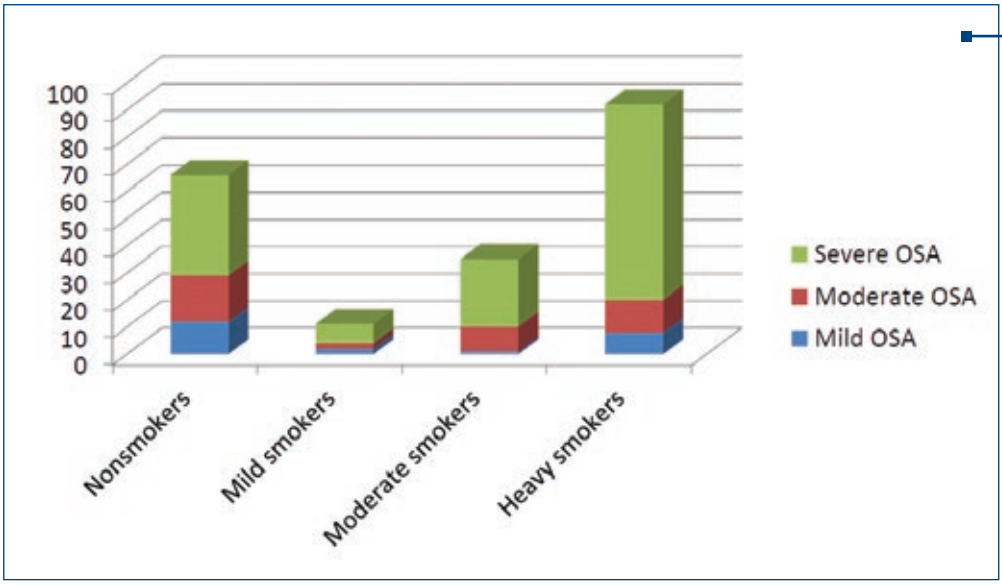

Figure 4. *Distribution of OSA cases (n=204) by severity and smoking*

According to ANOVA analysis of AHI and ODI means by smoking, performed in OSA patients without COPD, the values were significantly increased in smokers (n=50) versus nonsmokers (n=100) (F=32.417, p=0.000 for AHI, and F=29.417, p=0.000 for ODI), with no influence of BMI (F=3.786; p<0.06) – Table 3. The impact of COPD on the severity of OSA was also determined, according to AHI and ODI, revealing greater values in patients with OSA-COPD overlap (n=53) versus smokers with OSA, and no association of COPD (n=152) (F=97.88, p=0.000 for AHI and F=86.922, p= 0.000) – Table 4.

Disscussions

Smoking kills 6 persons every minute, and a fourth of smokers die of a tobacco-related illness[16]. Statistics showed, in 2002, 4 million deaths caused by smoking, including 1.2 million Europeans[17]. By 2020, this number will raise to 10 million smokers deaths annually[18]. The most affected are countries in transition and developing countries, due to factors such as trade liberalization, communications development and the globalization of tobacco industries. The first efforts to estimate the prevalence of smoking[19] were influenced by limited data from many developing countries. The most recent smoking prevalence estimations are based on several transversal studies performed between 1980 and 2012[20]. Smoked cigarettes number, worldwide, increased annually from 4.96 trillion in 1980 to 6.25 trillion in 2012, around 18 cigars as daily average[18]. The Romanian studies, conducted in the late 1990s and early 2000s, showed a high prevalence of smoking (44%), compared to other countries like Hungary (41.75%), Yemen (45%), Bosnia and Herzegovina (48%), Kenya (49%) and Namibia (50%)[21].

Smoking and OSA are two medical conditions with an increasing prevalence at the end of the 20th and the beginning of the 21st century, that interrelate systemic hypoxia and premature aging and close a vicious circle of important cardiovascular, cerebrovascular, respiratory and metabolic consequences and comorbidities, amplifying their mortality and morbidity[10]. The Wisconsin cohort study revealed in 1994 among active smokers "more chances" to snore and develop any form of OSA than nonsmokers[4]. Smoking prevalence in OSA patients was higher (n=138/204; 67.64%) versus 35% reported by Kashyap et al. in 2001[22] and 47.1% reported by Porebska et al. in 2014[23]. A meta-analysis by Vidya Krishnan et al. reported smoking as a risk factor for developing and worsening OSA, inducing longer latency to the onset of sleep, changes in the architecture of sleep during nighttime, difficult waking up in the morning and sleepiness during daytime[24].

Hypoxia is specific for both smoking and OSA, and chronic exposure to smoking is contributing to the severity of OSA[25]. Smokers with severe OSA have a greater cardiovascular risk by ischemic heart disease and resistant blood hypertension[17]. OSA-related smoking and OSA-COPD overlap syndrome are not sufficiently known by physicians, especially general practioners. The clinical implications of this study consist in the mandatory TSE questionaire in all sleep breathing disorders and mainly in OSA smokers (with or without COPD), revealing the impact of smoking on OSA severity even in patients without COPD or obesity. Tobacco cessation must be recommended to all smokers, but most of all to those with sleep complaints.

Conclusions

Obstructive sleep apnea prevalence and its severity seem to be related with smoking, having a significant risk of occurence according to heavy smoking history. ■

Table 3 The distribution of AHI, ODI and BMI mean values among patients with OSA and no COPD associated.

OSA without COPD		AHI	ODI	BMI
1 = smokers	N	50	50	50
	Mean	49.32	53.08	36.03
	Std. Deviation	22.629	25.8326	7.05068
	Variance	512.059	667.322	49.712
2 = nonsmokers	N	100	100	100
	Mean	42.47	43.308	34.169
	Std. Deviation	25.424	25.6124	6.81788
	Variance	646.373	655.995	46.483
Study population (+/-OSA)	Mean	33.01	34.606	33.7368
	Std. Deviation	27.088	29.2770	6.51249
	Variance	733.766	857.142	42.413

Table 4 The distribution of AHI, ODI and BMI mean values among smokers with OSA by COPD association

Smokers with OSA		AHI	ODI	Pack year	BMI
1 = OSA-COPD Overlap	Nr of cases	53	53	53	53
	Mean	49.53	52.387	25.26	36.2709
	Std. Deviation	21.555	29.5217	12.651	5.95187
	Variance	464.639	871.528	160.044	35.425
2= No COPD	Nr of cases	152	152	152	152
	Mean	44.37	46.183	12.01	34.8165
	Std. Deviation	24.764	26.0908	12.460	6.89126
	Variance	613.241	680.731	155.245	47.489
Study population (+/-OSA)	Nr of cases	326	326	326	326
	Mean	33.01	34.606	14.24	33.7368
	Std. Deviation	27.088	29.2770	13.591	6.51249
	Variance	733.766	857.142	184.706	42.413

References

1. Boișteanu D, Hăulica I, Simionescu V, Wirth JA. *Medicina Somnului*, Ed. Medicală, București, 2009.
2. Hobson JA. *Sleep* (Scientific American Library Series). 3rd printing ed. New York, NY: Holt, Henry and Company; 1989.
3. Jung R, Kuhlo W. Neurophysiological Studies of Abnormal Night Sleep and the Pickwickian Syndrome. *Prog Brain Res*. 1965; 18:140–59.
4. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med*. 1994; 154: 2219-24.
5. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet*. 1981; 1:862–5.
6. BaHammam AS, Alrajeh MS, Al-Ibrahim FS, Arafah MA, Sharif MM. Prevalence of symptoms and risk of sleep apnea in middleaged Saudi women in primary care. *Saudi Med J*. 2009; 30:1572–6.
7. Bogdan MA. *Pneumologie*, Ed. Universitară „Carol Davila", București, 2008, 443-454.
8. Fishman PA, Elias JA, Fishman JA, Grippi MA, Senior RM, Pack AI. Fishman's pulmonary disease and disorders, fourth edition,1697-1725.
9. Mihăicuță S. *Curs practic de somnografie*, Ed. Victor Babeș, Timișoara, 2010.
10. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*. 2008; 31(8):1071-1078.
11. Schrand JR. Is sleep apnea a predisposing factor for tobacco use? *Med Hypotheses*. 1996;47(6): 443 -8.
12. Rechtschaffen A, Kales A. A manual of standardised terminology: techniques and scoring systems for sleep stages of human subjects. Washington DC, National Institutes of Health, 1968 (publication No. 204).
13. American Academy of Sleep Medicine Task Force Report. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22:667–689.
14. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien IL: *American Academy of Sleep Medicine*, 2014.
15. Berry RB, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV; for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules,Terminology and Technical Specifi cations, Version 2.0.3. Darien,L: *American Academy of Sleep Medicine* 2014.
16. World Health Organization. Tobacco or Health: A Global Status Report. Geneva, Switzerland: World Health Organization; 1997.
17. http:// ec.europa.eu/health-eu/my_lifestyle/ tobacco/index_en.htm, Accessed at: 15-09-2011.
18. http://www.who.int/tobacco/global_report /2013/en/. Accessed December 9, 2013.
19. Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. *Tob Control*. 1994; 3(3):242-247.
20. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA*. 2014 Jan 8; 311(2):183-92.
21. Fumatul și sănătatea publică în România. Cunoștințe, atitudini și practici legate de consumul de tutun în rândul populației generale din România. CPSS, 2004.
22. Kashyap R, Hock LM, Bowman TJ. Higher prevalence of smoking in patients diagnosed as having obstructive sleep apnea. *Sleep Breath* 2001 Dec;5(4):167-72.
23. Porebska I, Kosacka M, Choła J, Gładka A, Wnek P, Brzecka A, Jankowska Renata.Smoking among patients with obstructive sleep apnea syndrome-preliminary report. *Pol Merkur Lekarski* 2014 Nov; 37(221):265-8.
24. Vidya K, Dixon-Williams S and Thornton JD. Where There Is Smoke…There Is Sleep Apnea. Exploring the Relationship Between Smoking and Sleep Apnea. *Chest* 2014;146 (6): 1673 - 1680.
25. Casasola GG, Alvarez-Sala JL, Marqués JA, Sánchez Alarcos JM, Tashkin DP, Espinos D. Cigarette smoking behavior and respiratory alterations during sleep in a healthy population. *Sleep Breath* 2002; 6:19-24
26. Lavie L, Lavie P. Smoking interacts with sleep apnea to increase cardiovascular risk. *Sleep Med*. 2008; 9:247-53.